UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/466,935	12/20/1999	VITALIY ARKADYEVICH LIVSHITS	US-126O	1750

38108 7590 02/01/2008

CERMAK & KENEALY LLP
ACS LLC
515 EAST BRADDOCK ROAD
SUITE B
ALEXANDRIA, VA 22314

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
02/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/2/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] In view of the appeal brief filed on 11/19/07, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

[2] Claims 77-84 are pending in the application.

[3] Receipt of an information disclosure statement, filed on 1/2/08, is acknowledged.

[4] Appellant's arguments in the Appeal Brief filed on 11/19/07 ("Brief") in response to the Final Office action mailed on 4/16/07 have been fully considered and are addressed below.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[6] The reference cited in the IDS filed on 1/2/08 has been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Claim Rejections - 35 USC § 102

[7] The rejection of claims 77-84 under 35 U.S.C. 102(b) as anticipated by Kobayashi et al. (*J Biochem* 98:1007-1016, 1985; "Kobayashi") as evidenced by Zakataeva et al. (*FEBS Lett* 452:228-232, 1999; "Zakataeva") and Kruse et al. (*Appl Microbiol Biotechnol* 59:205-210, 2002; "Kruse") is withdrawn – not in view of applicant's arguments – but upon further consideration and in favor of the rejection(s) under 35 U.S.C. 103(a) set forth below.

Claim Rejections - 35 USC § 103

[8] Claims 77-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (*supra*) in view of Williams et al. (US Patent 5,589,364; "Williams") and as evidenced by Zakataeva (*supra*) and Hanko et al. (*Analytical Biochem.* 324:29-38, 2004; "Hanko").

The claims are drawn to a method for producing an L-amino acid by: A) culturing a bacterium transformed with a DNA encoding SEQ ID NO:4 in a culture medium; B)

removing solids including cells from the medium; and C) purifying said L-amino acid from the medium obtained in step B).

The following comments are provided to clarify claim interpretation. Regarding step B) of claim 77, the step of "removing solids including cells from the medium", it is noted that: 1) the term "removing" can be interpreted as "separating" such that any process whereby the solids of a culture medium are separated away from the liquid portion of the culture medium or vice versa would appear to be encompassed by this step; 2) step B) of claim 77 does not require removal of *all* solids from the medium, as long as at least two cells are removed or separated away from the liquid portion of the culture medium, the limitation of "removing solids including cells from the medium" would appear to be satisfied; 3) "the medium" from which solids are removed would appear to encompass a heterogeneous suspension of solids and liquid; and 4) this step encompasses removing or transferring a portion of the culture medium, comprising both solids *and* liquid.

Regarding step C) of claim 77, the step of "purifying said L-amino acid from the medium obtained in step B)", it is noted that: 1) as noted above, the "L-amino acid" of step C) is not required to have been produced as a result of cultivating the bacterium in step A) and encompasses an L-amino acid that is present in the culture medium prior to cultivation, *e.g.*, an L-amino acid present in the LB medium; 2) as noted above, "the medium obtained in step B)" is not required to have *all* solids removed, thus, "the medium obtained in step B)" from which the L-amino acid is purified can be a mixture of solids and liquid, requiring only that at least two cells be removed or separated prior to

"purifying said amino acid"; 3) the L-amino acid that is purified in step C) is not limited to being *in the medium* and can instead be intracellular, *i.e.,* inside the bacterium, which is itself in the culture medium; and 4) purification is a term of degree and there is no recited or required level of purification of the L-amino acid in the method step.

The reference of Kobayashi teaches an *Escherichia coli* host cell transformed with vectors pAB104 and pA1042, wherein the vectors comprise a segment of the *E. coli* chromosome comprising the region between and including at least a portion of genes *pldA* and *pldB* (p. 1012, Figure 4 and p. 1014, Figure 6). Kobayashi teaches culturing this host cell in LB broth, followed by spinning down the cells, washing the cells with saline and preparing a cell extract by sonication (p. 1009, left column, bottom).

Kobayashi teaches the "Cells were spun down", which one of ordinary skill in the art would recognize as meaning that the cell culture was centrifuged to separate the culture medium into solids including cells and liquid, wherein the centrifugation occurs over a period of several seconds or minutes and over the time of centrifugation the liquid portion of the culture medium would gradually become clarified due to the removal of the solids. See, *e.g.,* the reference of Williams, which discloses centrifuging an *E. coli* culture for 10 minutes (column 36, lines 8-15). One of ordinary skill in the art would have further recognized that during centrifugation of a culture medium, the cells suspended in the liquid portion of the culture medium become are forced to the bottom of a centrifuge tube or bottle and become lodged as a "cell pellet", while the liquid portion of a culture medium remains above the cell pellet.

Kobayashi does not *expressly* teach purification of an L-amino acid including L-threonine.

The reference of Zakataeva is cited in accordance with MPEP 2124 to show that vectors pAB104 and pA1042 of Kobayashi comprise SEQ ID NO:3 and 1, corresponding to *E. coli rhtC* and *rhtB* genes, respectively. Zakataeva teaches *E. coli rhtC* and *rhtB* genes (corresponding to SEQ ID NO:3 and SEQ ID NO:1, respectively) fall between the *pldA* and *pldB* genes in the genome of *E. coli* (p. 229, Figure 1). As such, vector pAB104 or pA1042 of Kobayashi, which comprises a segment of the *E. coli* chromosome comprising the region between and including at least a portion of genes *pldA* and *pldB* as noted above, would necessarily comprise the *E. coli rhtC* and *rhtB* genes.

The reference of Hanko is cited in accordance with MPEP 2124 as showing that LB medium comprises L-amino acids, including L-threonine. Hanko teaches a determination of L-amino acids in LB broth, wherein LB broth is shown to have glutamine, asparagine, alanine, threonine, glycine, valine, serine, proline, isoleucine, leucine, methionine, histidine, phenylalanine, glutamate, aspartate, cysteine, tyrosine, and tryptophan (see, *e.g.,* p. 36, Figure 4).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to practice the method of Kobayashi, which involves culturing the host cell of Kobayashi (step A) of claim 77) and to centrifuge the resulting culture medium, comprising a heterogeneous mixture of cells and liquid, which would encompass both of

steps B) and C) of claim 77 based on the following claim interpretation, which is based on the "L-amino acid" of step C) being a component of the LB broth.

One can reasonably consider the earliest point in the centrifugation where as few as two cells are separated or removed from the liquid portion of the culture medium by centrifugal force to be the step of "removing...cells from the medium" of step B), wherein the remaining culture medium absent the at least two cells is an unseparated mixture of cells and liquid and this unseparated mixture is the "medium obtained in step B)." When the solids including cells of the remaining culture medium are considered to be a contaminant, at any point in the centrifugation *after* removing the at least two cells, the amino acid of the LB medium is necessarily purified from the solids present in the "medium obtained in step B)", thus satisfying the limitations of step C).

One would have been motivated to culture the cell of Kobayashi and centrifuge the resulting culture medium because this is expressly taught the Kobayashi reference. One would have had a reasonable expectation of success motivated to culture the cell of Kobayashi and centrifuge the resulting culture medium because this is expressly taught the Kobayashi reference because of the results of Kobayashi. By practicing such a method, this would necessarily result in purifying L-amino acids remaining from the LB broth in the culture medium. Therefore, claims 77-84, drawn to a method of producing an L-amino acid as noted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[9] Claims 77-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (*supra*) in view of Williams (*supra*) and Kaplan et al. (*J. Biol. Chem.* 240:3928-3933, 1965; "Kaplan") and as evidenced by Zakataeva (*supra*) and Kruse (*supra*).

The claims are drawn to a method for producing an L-amino acid by: A) culturing a bacterium transformed with a DNA encoding SEQ ID NO:4 in a culture medium; B) removing solids including cells from the medium; and C) purifying said L-amino acid from the medium obtained in step B). See the above comments regarding clarification of claim interpretation.

The teachings of the references of Kobayashi and Williams and evidentiary reference Zakataeva are set forth above. Kobayashi does not *expressly* teach purification of an L-amino acid including L-threonine.

The reference of Kaplan is cited as showing that it was well-known at the time of the invention that *E. coli* produces L-threonine. The reference of Kruse is cited in accordance with MPEP 2124 as showing that *E. coli* produces intracellular L-threonine and secretes L-threonine into a culture medium (p. 205, column 1 and p. 207, Figure 2).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to practice the method of Kobayashi, which involves culturing the host cell of Kobayashi (step A) of claim 77), centrifuge the resulting culture medium (step B) of claim 77), and prepare a cell-free extract from the isolated cells (step C) of claim 77) based on the following claim interpretation, wherein the "L-amino acid" of step C) is intracellular to the *E. coli* of Kobayashi or is secreted by the *E. coli* Kobayashi.

One would have reasonably considered the earliest point in the centrifugation where as few as two cells are separated or removed from the liquid portion of the culture medium by centrifugal force to be the step of "removing...cells from the medium" of step B), wherein the remaining culture medium absent the at least two cells is an unseparated mixture of cells and liquid and this unseparated mixture is the "medium obtained in step B)."

When the "L-amino acid" of step C) is intracellular, *i.e.,* inside the *E. coli* cell, then further centrifugation after removing the at least 2 cells, harvesting the cells, and preparing a cell extract to remove cellular debris is considered to be purifying the intracellular L-amino acid from the "medium obtained in step B)", thus satisfying the limitations of step C).

When the solids including cells of the remaining culture medium are considered to be a contaminant, at any point in the centrifugation *after* removing the at least two cells, the amino acid secreted by the *E. coli* of Kobayashi is necessarily purified from the solids present in the "medium obtained in step B)", thus satisfying the limitations of step C).

One would have been motivated to culture the cell of Kobayashi and centrifuge the resulting culture medium and optionally prepare a cell extract because this is expressly taught the Kobayashi reference. One would have had a reasonable expectation of success motivated to culture the cell of Kobayashi and centrifuge the resulting culture medium and optionally prepare a cell extract because of the results of the Kobayashi reference. By practicing such a method, this would necessarily result in

purifying intracellular L-amino acids in the *E. coli* of Kobayashi or would necessarily result in purifying secreted L-amino acids from the *E. coli* of Kobayashi. Therefore, claims 77-84, drawn to a method of producing an L-amino acid as noted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[10] Claim(s) 77-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (*supra*) in view of Kaplan (*supra*), Georgiou et al. (US Patent 5,508,192; "Georgiou"), and Begot et al. (*J. Microbiol. Methods* 25:225-232, 1996; "Begot") as evidenced by Zakataeva (*supra*) and Kruse (*supra*).

The claims are drawn to a method for producing an L-amino acid by: A) culturing a bacterium transformed with a DNA encoding SEQ ID NO:4 in a culture medium; B) removing solids including cells from the medium; and C) purifying said L-amino acid from the medium obtained in step B).

The teachings of Kobayashi and Kaplan and evidentiary references Zakataeva and Kruse are set forth above. Kobayashi further teaches culturing the *E. coli* host cell transformed with vector pAB104 and pA1042 "to the middle-exponential phase in LB broth" prior to spinning down the cells and preparing a cell extract thereof (p. 1009, left column, bottom). Kobayashi does not *expressly* teach a step of purifying an L-amino acid.

Although not specifically disclosed by Kobayashi, at the time of the invention a well-known method for determining the growth phase of a bacterial culture medium was to monitor the optical density of the culture medium by transferring a small portion of a

culture medium to a cuvette for measurement using a spectrophotometer. See particularly Begot at p. 226, paragraph bridging columns 1-2). For example, Georgiou teaches culturing of an *E. coli* host cell in LB medium in a shake flask and that middle exponential phase of *E. coli* is reached at an optical density at 600 nm between 0.3-0.4 (column 18, lines 50-53). To measure the optical density of a culture medium, it was well known in the art to transfer a small portion of the culture medium to a cuvette for measurement using a spectrophotometer.

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Kobayashi, Begot, and Georgiou to culture the host cell of Kobayashi (step A) of claim 77), remove a portion of the cell culture, which would include cells, for measurement of optical density (step B) of claim 77), spin down the cells from the remaining culture medium upon achieving growth to middle-exponential phase, and optionally prepare a cell extract of the harvested cells (step C) of claim 77) based on the following claim interpretation, wherein the "L-amino acid" of step C) is intracellular to the *E. coli* of Kobayashi or is secreted by the *E. coli* Kobayashi.

One would have reasonably considered removing a portion of the culture medium for optical density measurement to be encompassed by a step of "removing...cells from the medium" of step B), wherein the remaining culture medium is the "medium obtained in step B)."

When the "L-amino acid" of step C) is intracellular, *i.e.,* inside the *E. coli* cell, then centrifugation after removing the portion of cells for optical density measurement and preparing a cell extract to remove cellular debris is considered to be purifying the

intracellular L-amino acid from the "medium obtained in step B)", thus satisfying the limitations of step C).

When the solids including cells of the remaining culture medium are considered to be a contaminant, then centrifugation after removing the portion of cells for optical density measurement is necessarily purifying L-amino acids from the solids including cells present in the "medium obtained in step B)", thus satisfying the limitations of step C).

One would have been motivated to culture the host cell of Kobayashi, remove a portion of the cell culture, which would include cells, for measurement of optical density, spin down the cells from the remaining culture medium upon achieving growth to middle-exponential phase, and optionally prepare a cell extract of the harvested cells because of the teachings of Kobayashi, Begot, and Georgiou. One would have had a reasonable expectation of success to cultivate the host cell of Kobayashi, remove a portion of the medium for measurement of optical density, centrifuge the cells and optionally prepare a cell extract of the harvested cells because of the results of Kobayashi, Begot, and Georgiou. By practicing such a method, this would necessarily result in purifying intracellular L-amino acids in the *E. coli* of Kobayashi or would necessarily result in purifying secreted L-amino acids from the *E. coli* of Kobayashi. Therefore, claims 77-84, drawn to a method of producing an L-amino acid as noted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

Claim Rejections – Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[11] Claims 77-84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 6-7 of co-pending Application No. 11/106,455. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because: claims 77-78 and 81-82 of the instant application are generic to all that is recited in claims 4 and 6-7 of the co-pending application. Also, claims 79-80 and 83-84 cannot be considered patentably distinct over

claims 4 and 6-7 of the co-pending application when there is a specifically disclosed embodiment in the co-pending application that supports claims 4 and 6-7 of the co-pending application and falls within the scope of claims 79-80 and 83-84 herein because it would have been obvious to one having ordinary skill in the art for the "DNA of part a) or b) of claim 4 to be a DNA comprising both *rhtB* and *rhtC* the methods of claims 4 and 6-7 because that is a specifically disclosed embodiment that supports such a claimed method (see particularly the specification at p. 21, Table 5, NZ10/pRhtBC). One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a specifically disclosed embodiment within claims 4 and 6-7 of the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is acknowledged that the 11/106,455 application is filed as a divisional application of 09/466,935 and that, according to MPEP 804.01, "[t]he third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent." However, it is noted that the restriction requirement between product and method claims in this application was withdrawn in the Office action mailed on 8/10/05 and according to MPEP 804.01.(E), the prohibition against a double patenting rejection does not apply where "[t]he requirement for restriction was withdrawn by the examiner before the patent issues." As such, the

provisional obviousness-type double patenting rejection is proper.

Conclusion

[12] Status of the claims:

Claims 77-84 are pending.

Claims 77-84 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

MANJUNATH RAO
SUPERVISORY PATENT EXAMINER